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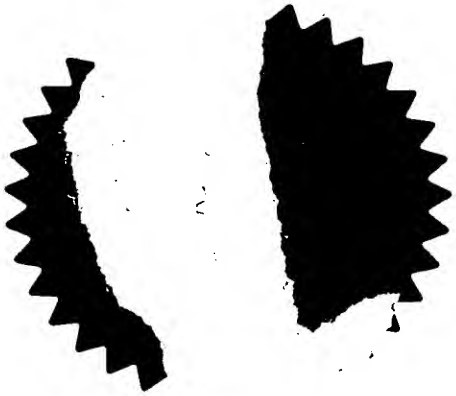

Signed A W Brewer

Dated 8 November 2000

For official use

14FEB00 E512891-1 D01298
P01/7700 0.00-0003234.2

11 FEB 2000

Your reference
PCS10901JRH-PROV

0003234.2

11 FEB 2000

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The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

METHOD OF TREATMENT

2 Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED

Country *(and State of incorporation, if appropriate)*
UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases,** please give the following details:

Address
RAMSGATE ROAD
SANDWICH
KENT

UK postcode CT13 9NJ
(if applicable)

Country UNITED KINGDOM

ADP number
(if known) 6892673001

2d, 2e and 2f:
If there are further applicants please provide details on a separate sheet of paper.

Second applicant (if any)

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

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Forenames

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3
An address for service in the United Kingdom must be supplied.
Please mark correct box

3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ *go to 3b*

⬇ *Please give details below*

Agent's name
MR. JAMES R. HAYLES
Agent's address
PFIZER LIMITED
RAMSGATE ROAD
SANDWICH
KENT
Postcode CT13 9NJ

Agent's ADP number 6409593002

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

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4 Reference number

4 Agent's or applicant's reference number *(if applicable)* PCS10901JRH-PROV

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ *go to 6*

⬇ *please give details below*

☐ number of earlier application or patent number

☐ filing date *(day month year)*

☐ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

6

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

7

The answer must be 'No' if:
- *any applicant is not an inventor*
- *there is an inventor who is not an applicant, or*
- *any applicant is a corporate body.*

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark the correct box

Yes ☐ No ☒ ➡

A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77	
Claim(s) 2	Description 13
Abstract	Drawing(s)

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 - Preliminary Examination/Search	
Patents Form 10/77 - Request for Substantive Examination	

9

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9 Request

I/We request the grant of a patent on the basis of this application.

Please sign here ➡

Signed James Hayles Date 07/02/2000

(day month year)

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Method of treatment

This invention relates to the use of certain endothelin antagonists in the treatment of companion animals suffering from conditions mediated by endothelin.

Endothelin (ET) is a potent vasoconstrictor synthesised and released by endothelial cells. There are three distinct isoforms of ET: ET-1, ET-2 and ET-3, all being 21-amino acid peptides and herein the term 'endothelin' refers to any or all of the isoforms. Two receptor subtypes, ET_A and ET_B have been pharmacologically defined (see for example H. Arai et al, Nature, **348**, 730 , 1990) and further subtypes have recently been reported. Stimulation of ET_A promotes vasoconstriction, and stimulation of ET_B receptors causes either vasodilation or vasoconstriction. The main effects of ET are observed in the cardiovascular system, particularly in the coronary, renal, cerebral and mesenteric circulation, and the effects of endothelin are often long-lasting. Stimulation of ET receptors also mediate further biological responses in cardiovascular and non-cardiovascular tissues such as cell proliferation and matrix formation.

Increased circulating levels of endothelin have been observed in patients who have undergone percutaneous transluminal coronary angioplasty (PTCA) (A.Tahara et al, Metab. Clin. Exp. **40**, 1235, 1991) and ET-1 has been found to induce neointimal formation in rats after balloon angioplasty (S.Douglas et al, J.Cardiovasc.Pharm., **22** (Suppl 8), 371, 1993). The same workers have found that an endothelin antagonist, SB-209670, causes a 50% reduction in neointimal formation relative to control animals (S.Douglas et al, Circ Res, **75**, 1994). Antagonists of the endothelin receptor may thus be useful in preventing restenosis post PTCA. The $ET_{A/B}$ receptor antagonist Bosentan reportedly decreased blood pressure in hypertensive patients (New Eng.J.Med. (1998) **338**, 784-790). Antagonists of ET_B receptors such as BQ-788 have been demonstrated to increase peripheral resistance in man (Hypertension (1999) **33**, 581-585). Thus ET_A-selective receptor antagonists are likely to be of benefit in hypertension.

Endothelin-1 is produced in the human prostate gland and endothelin receptors have been identified in this tissue (Eur. J.Pharmacol. (1988) **349**, 123-128). Since endothelin is a contractile and proliferative agent, endothelin antagonists could be useful in the treatment of benign prostate hypertrophy.

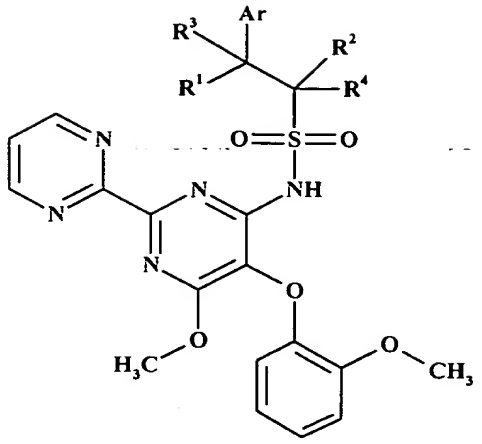
There is widespread localisation of endothelin and its receptors in the central nervous system and cerebrovascular system (R.K.Nikolov et al, Drugs of Today, **28**(5), 303, 1992) with ET being implicated in cerebral vasospasm, cerebral infarcts, septic shock, myocardial infarction and neuronal death.

Elevated levels of endothelin have also been observed in patients with:
- recurrent airway obstruction (Pulm.Pharm.Ther. (1998) **11**: 231-235);
- asthma (Am.J.Resp.Crit. Care Med. (1995) **151**:1034-1039);
- acute renal failure (K.Tomita, et al, Med.Philos. (1994) **13**(1), 64-66);
- chronic renal failure (F.Stockenhuber et al, Clin Sci (Lond.), **82**, 255, 1992);
- ischaemic Heart Disease (M.Yasuda, Am. Heart J., **119**, 801, 1990);
- stable or unstable angina (J.T.Stewart, Br. Heart J. **66**, 7 1991);
- pulmonary hypertension (D.J.Stewart et al, Ann. Internal Medicine, **114**, 464, 1991);
- congestive heart failure (R.J.Rodeheffer et al, Am.J.Hypertension, **4**, 9A, 1991);
- preeclampsia (B.A.Clark et al, Am.J.Obstet.Gynecol., **166**, 962, 1992);
- diabetes (A.Collier et al, Diabetes Care, **15** (8), 1038, 1992);
- Crohn's disease (S.H.Murch et al, Lancet, **339**, 381, 1992); and
- atherosclerosis (A.Lerman et al, New Eng. J. Med., **325**, 997, 1991).

Such diseases may be referred to as "endothelin-mediated disorders". Although the above discussion relates mainly to humans, corresponding disease states may be found in companion animals such as dogs, cats and horses. In every case the disease state associated with the physiologically elevated levels of endothelin is potentially treatable with a substance which decreases the effect of endothelin, such as an endothelin receptor antagonist, or a compound which binds endothelin such that it reduces the effective concentration thereof at the endothelin receptors.

It has now been found that a small group of endothelin receptor antagonist compounds are particularly useful in the treatment of endothelin-mediated disorders in companion animals (such as dogs, cats and horses).

Thus, according to the present invention, there is provided the use of a compound of formula I,



I

wherein R^1 and R^2 each represent H, or together represent a second carbon-carbon bond between the carbon atoms to which they are attached;

when R^1 and R^2 each represent H, then R^3 and R^4 also represent H;

when R^1 and R^2 together represent a second carbon-carbon bond between the carbon atoms to which they are attached, then R^3 and R^4 independently represent H or C_{1-6} alkyl;

Ar represents:

phenyl or naphthyl, which groups are optionally substituted by one or more groups selected from C_{1-6} alkyl [which may itself be substituted by one or more substituents selected from halo, C_{1-6} alkoxy, CO_2H, NH_2, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl$)_2$], halo, C_{1-6} alkoxy, CO_2H, C_{1-6} alkoxycarbonyl, NO_2, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, OH and C_{1-3} alkylenedioxy, or

a 5- or 6-membered heteroaryl ring containing up to 4 heteroatoms selected from N, O and S, which group is optionally substituted by one or more groups selected from C_{1-6} alkyl [which may itself be substituted by one or more substituents selected from halo, C_{1-6} alkoxy, CO_2H, NH_2, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl$)_2$], halo, C_{1-6} alkoxy, CO_2H, C_{1-6} alkoxycarbonyl, NO_2, CN, NH_2, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl$)_2$;

or a veterinarily acceptable salt thereof;

in the manufacture of a medicament for the treatment or prophylaxis of an endothelin-mediated disorder in a companion animal.

Veterinarily acceptable salts include alkali and alkaline earth metal salts (for example sodium and potassium salts), and salts formed with basic amines (for example, tri(C_{1-6} alkyl)-substituted amines).

Preferred features of the invention include:

(a) the companion animal is a cat, a dog or a horse (most preferably a dog);

(b) the endothelin-mediated disorder is hypertension, congestive heart failure or chronic renal failure (most preferably congestive heart failure);

(c) R^1 and R^2 each represent H;

(d) R^3 and R^4 each represent H; and

(e) Ar represents phenyl, naphthyl or thienyl, which groups are optionally substituted by one or more groups selected from C_{1-6} alkyl, halo, CF_3, C_{1-6} alkoxy, CO_2H and C_{1-6} alkoxycarbonyl - most preferably, Ar is phenyl.

Compounds of formula I in which R^1 and R^2 each represent H are disclosed in International Patent Application WO 98/57938. Compounds of formula I in which R^1 and R^2 together represent a second carbon-carbon bond between the carbon atoms to which they are attached are disclosed in European Patent Application 882719.

The compound of formula I in which R^1, R^2, R^3 and R^4 each represent H, and Ar is phenyl is N-[6-methoxy-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]-2-phenylethansulphonamide. It is disclosed in Example 1 of International Patent Application WO 98/57938, is referred to herein as "dihydro-YM-598", and is of particular interest.

The compound of formula I in which R^1 and R^2 together represent a second carbon-carbon bond between the carbon atoms to which they are attached, R^3 and R^4 each represent H, and Ar is phenyl is N-[6-methoxy-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]-2-phenylethensulphonamide. It is disclosed in Example 2 of European Patent Application 882719, is referred to herein as "YM-598", and is of particular interest.

The invention has the advantage that the compounds of formula I have a longer duration of action than the compounds of the prior art. This means that the frequency with which they must be administered will be reduced. This is particularly important with veterinary medicines, because animals often resist administration of medicaments. Therefore, the reduced administration frequency will lead to more regular treatment (enhancing disease control) and greater convenience (enhancing patient compliance).

The biological activity of the compounds of formula I (and some comparator compounds) was assessed in the following tests.

Test A

Inhibition of contraction induced by ET-1 in dog renal artery strips to generate K_b values

A K_b value is a measure of functional activity, and this is taken to be the free plasma concentration of a test compound required to provide efficacy.

Renal arteries from beagle dogs (body weight 9-15 kg) were cut into spirals and divided into 5 mm long strips. The side of each strip that was adjacent to the lumen of the vessel was gently rubbed to remove the endothelium. Each strip was mounted under a resting tension of 1.2g in an organ bath containing Krebs-Henseleit solution at 37°C gassed with 5% CO_2 in 95% O_2. The tension generated by each strip was recorded isometrically. After incubating the tissues with test compound for 75 minutes, cumulative concentration response curves were constructed to ET-1 in the presence of 10μM Bestatin, 10μM Captopril, 10μM Thiorphan, 50μM indomethacin and 0.001% BSA. Only a single ET-1 curve was constructed in each tissue and tension increases expressed as a percentage of the response to 120mM KCl determined before the addition of the test compound. The antagonistic activity of the test compound was determined by calculating the apparent K_b for a single concentration of each compound using the method described by MacKay (J. Pharm. Pharmac. 30, 321-313, 1978). The concentration of ET-1 causing 50% of the maximum response (EC_{50}) was calculated and from these the dose ratio (DR). This is the ratio of the EC_{50} in the presence of the test compound divided by the EC50 in its absence. The DR is then put into the following equation:

$$\text{apparent } pK_b = \log(DR-1) - \log[B] \qquad \text{(where B = molar concentration of test compound)}$$

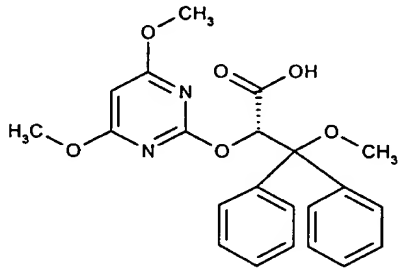
$$\text{apparent } K_b = \text{antilog } pK_b$$

Results

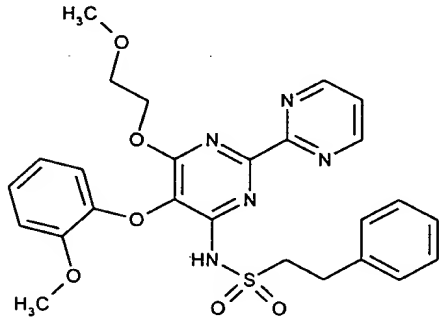
Compound	Apparent K_b (nM)
YM-598	58

LU 135,252[1]	111
Example 2, WO 98/57938[2]	136
dihydro-YM-598	86

(1) Structure of LU 135,252 (comparator compound) is:



(2) Structure of Example 2, WO 98/57938 (comparator compound) is:



Test B

Pharmacokinetic studies

In order to assess the potential of test ET_A antagonists to provide efficacy, a pharmacokinetic study in the dog was carried out. This was initially carried out with n=1 in order to provide an early indication of whether each compound has a good pharmacokinetic profile.

It is generally assumed that the fraction of drug that is free (i.e. unbound) in plasma is in equilibrium with free drug in other aqueous compartments of the body, provided the drug is able to cross membrane barriers. Hence, whilst the actual amount of drug in plasma may represent a small proportion of the drug in the body, it provides valuable information on the free concentration of the drug throughout the body. Assuming that only free drug is available to exert a pharmacological effect, then determining the free drug concentration in plasma and

combining this with knowledge of drug potency, provides a measure of the potential efficacy of that compound in vivo [see William J. Jusko and Mark Gretch, 'Plasma and tissue protein binding of drugs in pharmacokinetics', Drug Metabolism Reviews, 5(1), 43-140 (1976)].

(a) Analysis of Plasma Samples

Test compounds were administered to a dog by i.v. infusion over 10 minutes to give a dose of 0.5 mg/kg. Blood samples were taken at various time points and centrifuged to provide plasma samples. These samples were analysed using Mass Spectrometry to provide total plasma concentrations.

Plasma samples and standards (prepared using blank plasma spiked with the appropriate concentration of compound), were typically prepared by protein precipitation with acetonitrile (MeCN) [2:1 MeCN/plasma], centrifuged and the supernatant injected into a liquid chromatography/mass spectrum/mass spectrum (LC/MS/MS) system (PE Sciex API 365) running with the following conditions:

Flow rate: 1.0 ml/min

Column: Hypersil™ BDS C18, 5μm, 4.6mm i.d. x 50 mm.

Mobile Phase: (A) 5 mM ammonium acetate in 2% MeCN 98% H_2O

(B) 5mM ammonium acetate in 90% MeCN 10% H_2O

Gradient:

0.0 min	95% (A)	5% (B)
1.0 min	95% (A)	5% (B)
2.0 min	5% (A)	95% (B)
4.0 min	5% (A)	95 % (B)
6.5min	95% (A)	5% (B) First 2.5 minutes diverted to waste, the remainder to MS

Injection volume of supernatant prepared above: 150 μl

MS Mode: Ionspray, positive ion, MRM

Dwell time: 500 msec. Pause time: 50 msec

Collision gas setting: 1 Ion energy: optimised for each compound

Total plasma concentrations in the dog were determined by comparison with the standard line constructed (using the spiked plasma samples) to cover the expected concentration range.

Results

Compound	Total plasma concentration at 24 hours (nM) following 0.5 mg/kg iv dose
YM-598	1161 (25 h)
LU 135,252	40
Example 2, WO 98/57938	<93
dihydro-YM-598	466

(b) Determination of plasma protein binding by equilibrium dialysis

The methods used are based on the principles outlined by Pacifici and Viani ['Methods of determining plasma and tissue binding of drugs', Clinical Pharmacokinetic Concepts 23 (6), 449-468 (1992)]. An example of a method used is described below.

Plasma containing the test compound was placed in a chamber (half-cell), separated by a semi-permeable membrane (Spectra/Por™ 1 47 mm diam MWCO 6-8000) from isotonic buffer at physiological pH in the other half-cell. The system was allowed to equilibrate, such that low molecular weight compounds distributed evenly between the two chambers (plasma and buffer), whilst high molecular weight molecules were restricted to the plasma chamber. At equilibrium the concentration of the unbound test compound is the same on either side of the membrane. The concentration of total test compound in each half-cell was then determined (using essentially the described above) and the extent of plasma protein binding calculated.

The Spectra/Por™ Equilibrium Dialyzer used to determine protein binding was supplied by NBS Biologicals.

Results

Compound	Plasma protein binding (%, canine)
YM-598	87
LU 135,252	96.8
Example 2, WO 98/57938	88
dihydro-YM-598	91

(c) Calculation of free plasma concentrations

$$\text{Fraction unbound (Fu)} = \frac{\text{concentration in buffer}}{\text{concentration in plasma}}$$

or % protein bound = (1-Fu)x 100

The free plasma concentrations of the compound can then be determined.

Free plasma concentration = total plasma concentration (from method 1) x fraction unbound (from method 2)

Results

Compound	Free concentration at 24 hours (nM) following 0.5 mg/kg i.v. dose
YM-598	151 (25 h)
LU 135,252	1.3
Example 2, WO 98/57938	<11
dihydro-YM-598	41.9

From the above data, the free plasma concentration found may be expressed as a percentage of the free plasma concentration of the test compound required to provide efficacy (K_b value, from Test A above), and by multiplying by 4, the percentage of K_b may be estimated for a 2.0 mg/kg dose (a dose likely to be used in practice):

Compound	% of K_b at 24 hours following 0.5 mg/kg i.v. dose	Estimated % of K_b at 24 hours following 2.0 mg/kg i.v. dose
YM-598	260	1040
LU 135,252	1.2	4.8
Example 2, WO 98/57938	<8	<32
dihydro-YM-598	49	196

From the above table, it can be seen that only YM-598 and dihydro-YM-598 would still be efficacious after 24 hours following a 2.0 mg/kg i.v. dose (because they would be present at 100% of the K_b value or more).

Test C

Inhibition of ET-1-induced pressor response in conscious beagle dogs

Studies were performed in surgically prepared conscious beagle dogs (13-17 kg) which were well adjusted to the laboratory environment. Surgical preparation was performed under recovery anaesthesia to insert an indwelling aortic catheter with external access between the scapulae and protruding subcutaneous ECG studs, positioned for the recording of lead II electrocardiograms. During studies dogs were placed, unrestrained, in "Pavlov" type slings. The aortic catheter was connected to a pressure transducer for the measurement of systemic arterial pressure and ECG studs, via patient cables, to a bio-amplifier for the recording of electrocardiograms. ET-1 was administered as a 15 min infusion (25 pmoles/kg/min) via a temporary catheter inserted into the saphenous vein. Test compound or placebo was administered by oral gavage (0.5 or 2.0 mg/kg) at 1 and 24 hours prior to the infusion of ET-1. Individual studies investigated no more than a single dose of test compound or placebo at any one time. Systemic arterial pressure and electrocardiograms were recorded for one hour prior to and one hour after the start of the infusion of ET-1. Test compounds were evaluated by comparing the effects of placebo or test compound on the magnitude of pressor response elicited by ET-1.

Oral administration of test compounds exhibited an excellent suppressive action on the ET-1-induced pressor responses in conscious dogs. The changes in arterial pressure (mmHg) are shown in the following tables:

Time	Dose	Placebo	YM-598	% inhibition
1 hour	0.5 mg/kg p.o.	18	7	57
24 hours	2.0 mg/kg p.o.	24	13	44

Time	Dose	Placebo	dihydro-YM-598	% inhibition
1 hour	0.5 mg/kg p.o.	17	3	76
24 hours	2.0 mg/kg p.o.	12	3	80

For treatment of companion animals such as dogs, the compounds of formula I, or their veterinarily acceptable salts, can be administered alone but will generally be administered in admixture with a pharmaceutical / veterinary carrier selected with regard to the intended route of administration and standard pharmaceutical / veterinary practice. For example they can be administered orally in the form of tablets containing such excipients as starch or lactose or in capsules or ovules either alone or in admixture with excipients or in the form of elixirs, solutions or suspensions containing the substance in a liquid carrier, for example a vegetable oil, glycerine or water with a flavouring or colouring agent. They can be injected parenterally, for example intravenously, intramuscularly or subcutaneously. For parental administration, they are best used as sterile aqueous solutions which may contain other substances, for example, enough glucose or salts to make the solution isotonic with blood. For parenteral administration the substance may also be administered as a solution or suspension in a suitable oil, for example polyethylene glycol, lecithin or sesame oil.

The substances may also be administered through inhalation of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane.

Alternatively the substances can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder or in the form of a medicated plaster, patch or membrane. For example they may be incorporated in a cream containing an aqueous emulsion of polyethylene glycols or liquid paraffin. The compounds may also be administered intranasally.

For veterinary use although it is possible to administer the substance directly without any formulation, they are preferably employed in the form of a pharmaceutical or veterinary formulation comprising a pharmaceutically or veterinarily acceptable carrier, diluent or excipient and an active substance. Such compositions will contain from 0.1 percent by weight to 90.0 percent by weight of the active ingredient.

The methods by which the substances may be administered include oral administration by capsule, bolus, tablet or drench, topical administration as an ointment, a pour-on, spot-on, dip, spray, mousse, shampoo or powder formulation or, alternatively, they can be administered by injection (e.g. subcutaneously, intramuscularly or intravenously), or as an implant. Administration methods chosen will reflect the condition to be treated, the animal to be treated, numbers to be treated, ease of operation, etc. according to standard veterinary practice.

Such formulations are prepared in a conventional manner in accordance with standard pharmaceutical or veterinary practice. Thus capsules, boluses or tablets may be prepared by mixing the active ingredient with a suitable finely divided diluent or carrier additionally containing a disintegrating agent and/or binder such as starch, lactose, talc or magnesium stearate, etc. Oral drenches are prepared by dissolving or suspending the active ingredient in a suitable medium. Pour-on or spot-on formulations may be prepared by dissolving the active ingredient in an acceptable liquid carrier vehicle such as butyl digol, liquid paraffin or a non-volatile ester, optionally with the addition of a volatile component such as propan-2-ol.

Alternatively, pour-on, spot-on or spray formulations can be prepared by encapsulation, to leave a residue of active agent on the surface of the animal. Injectable formulations may be prepared in the form of a sterile solution which may contain other substances, for example enough salts or glucose to make the solution isotonic with blood. Acceptable liquid carriers include vegetable oils such as sesame oil, glycerides such as triacetin, esters such as benzyl

benzoate, isopropyl myristate and fatty acid derivatives of propylene glycol, as well as organic solvents such as pyrrolidin-2-one and glycerol formal. The formulations are prepared by dissolving or suspending the active ingredient in the liquid carrier such that the final formulation contains from 0.1 to 10% by weight of the active ingredient.

These formulations will vary with regard to the weight of active substance contained therein, depending on the species of animal to be treated, the severity and type of infection and the body weight of the animal. For parenteral, topical and oral administration, typical dose ranges of the active ingredient are 0.01 to 100 mg per kg of body weight of the animal. Preferably the range is 0.1 to 10 mg per kg, more preferably 0.5 to 5 mg per kg, for example 2 mg per kg.

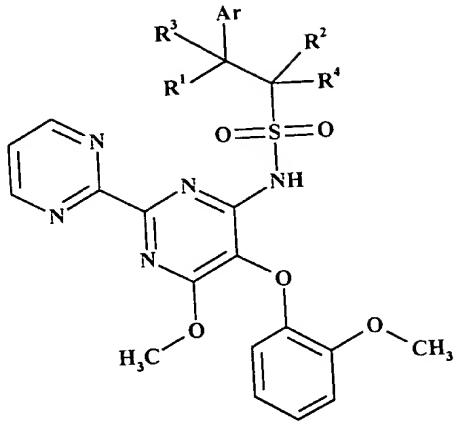
The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

As an alternative for veterinary use the substances may be administered with animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

Thus, the invention further provides a formulation containing a compound of formula I, as defined above, or a veterinarily acceptable salt thereof, characterized in that it is adapted for administration to a companion animal. Suitable formulations include those adapted for oral administration, having a taste attractive to the companion animal (for example containing a suitable flavouring agent).

Claims:

1. The use of a compound of formula I,



I

wherein R^1 and R^2 each represent H, or together represent a second carbon-carbon bond between the carbon atoms to which they are attached;

when R^1 and R^2 each represent H, then R^3 and R^4 also represent H;

when R^1 and R^2 together represent a second carbon-carbon bond between the carbon atoms to which they are attached, then R^3 and R^4 independently represent H or C_{1-6} alkyl;

Ar represents:

phenyl or naphthyl, which groups are optionally substituted by one or more groups selected from C_{1-6} alkyl [which may itself be substituted by one or more substituents selected from halo, C_{1-6} alkoxy, CO_2H, NH_2, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl$)_2$], halo, C_{1-6} alkoxy, CO_2H, C_{1-6} alkoxycarbonyl, NO_2, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, OH and C_{1-3} alkylenedioxy, or

a 5- or 6-membered heteroaryl ring containing up to 4 heteroatoms selected from N, O and S, which group is optionally substituted by one or more groups selected from C_{1-6} alkyl [which may itself be substituted by one or more substituents selected from halo, C_{1-6} alkoxy, CO_2H, NH_2, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl$)_2$], halo, C_{1-6} alkoxy, CO_2H, C_{1-6} alkoxycarbonyl, NO_2, CN, NH_2, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl$)_2$;

or a veterinarily acceptable salt thereof;

in the manufacture of a medicament for the treatment or prophylaxis of an endothelin-mediated disorder in a companion animal.

2. The use as claimed in claim 1, wherein the companion animal is as a cat, a dog or a horse.

3. The use as claimed in claim 1 or claim 2, wherein the endothelin-mediated disorder is hypertension, congestive heart failure or chronic renal failure.

4. The use as claimed in any one of the preceding claims, wherein R^1 and R^2 each represent H.

5. The use as claimed in any one of the preceding claims, wherein R^3 and R^4 each represent H.

6. The use as claimed in any one of the preceding claims, wherein Ar represents phenyl, naphthyl or thienyl, which groups are optionally substituted by one or more groups selected from C_{1-6} alkyl, halo, CF_3, C_{1-6} alkoxy, CO_2H and C_{1-6} alkoxycarbonyl;

7. The use as claimed in any one of the preceding claims, wherein Ar is phenyl.

8. A formulation containing a compound of formula I, as defined in claim 1, or a veterinarily acceptable salt thereof, characterized in that it is adapted for administration to a companion animal.

9. A formulation as claimed in claim 8, which is adapted for oral administration and has a taste attractive to the companion animal.

10. A method of treatment or prophylaxis of an endothelin-mediated disorder in a companion animal, which comprises administering an effective amount of a compound of formula I, as defined in claim 1, or a veterinarily acceptable salt thereof, to the companion animal.